Mast cell activation syndrome: Proposed diagnostic criteria

Cem Akin, MD, PhD,[a]* Peter Valent, MD,[b] and Dean D. Metcalfe, MD[c] *Ann Arbor, Mich, Vienna, Austria, and Bethesda, Md*

The term mast cell activation syndrome (MCAS) is finding increasing use as a diagnosis for subjects who present with signs and symptoms involving the dermis, gastrointestinal track, and cardiovascular system frequently accompanied by neurologic complaints. Such patients often have undergone multiple extensive medical evaluations by different physicians in varied disciplines without a definitive medical diagnosis until the diagnosis of MCAS is applied. However, MCAS as a distinct clinical entity has not been generally accepted, nor do there exist definitive criteria for diagnosis. Based on current understanding of this disease "syndrome" and on what we do know about mast cell activation and resulting pathology, we will explore and propose criteria for its diagnosis. The proposed criteria will be discussed in the context of other disorders involving mast cells or with similar presentations and as a basis for further scientific study and validation. (J Allergy Clin Immunol 2010;126:1099-104.)

Key words: *Mast cells, tryptase, histamine, mastocytosis, allergy, anaphylaxis, urticaria*

The last several years have witnessed an increasing use of the term mast cell activation syndrome (MCAS) as a diagnosis for subjects who present with signs and symptoms from flushing to hives, abdominal pain to diarrhea, and paresthesia to cognitive dysfunction (See Table E1 in this article's Online Repository at www.jacionline.org for an example of what is available to the lay public)[1] and where an extensive medical evaluation has failed to result in a definitive diagnosis. Although MCAS as a distinct clinical entity has not yet been recognized or defined by means of definitive criteria for diagnosis, there have been scientific publications on the subject, even relating to a possible genetic basis of a "mast cell mediator syndrome."[2] This article will explore the evolution of the application of the term MCAS and propose criteria for its diagnosis in the context of other disorders involving mast cells or with similar presentations and as a basis for further scientific discussion, study, and validation.

Abbreviations used
MCAS: Mast cell activation syndrome
MMAS: Monoclonal mast cell activation syndrome
SCF: Stem cell factor
UP: Urticaria pigmentosa
WHO: World Health Organization

HISTORICAL PERSPECTIVE

In the late 1980s, the existence of "mast cell activation disorders" apparently associated with sudden synchronous mediator release in the absence of evidence of mast cell proliferation began to be discussed in the literature.[3] The possibility of such disorders, which would have as their basis activated mast cells, was considered at a consensus conference to classify variants of systemic mastocytosis. To quote, "There also may be unknown diseases of mast cell activation, in which mast cells either activate at a lower threshold of stimulation, or perhaps resist the usual stimuli to degranulate,"[4] rather than, for example, a variable sensitivity to histamine.[5] In the same conference it was suggested that such "systemic mastocyte activation" could be documented biochemically.[6] The possibility of such a syndrome would explain signs and symptoms that appear to suggest a patient has a mast cell proliferative disorder but with the diagnostic criteria for this disease remaining unmet.[7]

In the diagnosis of MCAS, patients with such signs and symptoms as flushing, itching, unexplained gastrointestinal disturbances, and unexplained fluctuations in blood pressure (see Table E1) usually are first evaluated by an internist, pediatrician, or family practitioner, at which time common causes of such symptoms are eliminated. The patient might then be referred for an evaluation to determine whether there is an allergic basis for the presentation. If the results of this workup are negative, it is then logical to consider whether the patient might have an unrecognized mast cell proliferative disorder.[7] If the result of an evaluation for systemic mastocytosis is negative, one possibility to consider is that the patient has a mast cell–based disease but one in which the mast cell population is not increased in number, as would be seen in a mast cell proliferative disorder. Rather, the mast cell population is hyperresponsive.

Proof of concept of the possibility of hyperactive mast cells contributing to disease states is supported by accumulation of data surrounding the acceptance of the designation monoclonal mast cell activation syndrome (MMAS) by a consensus conference to describe patients who experience unprovoked episodes of hypotension and have met 1 or 2 minor diagnostic criteria for mastocytosis but lack the full expression of the phenotype (3 minor or 1 major and 1 minor criteria).[8] The recognition of MMAS followed reports that patients with mastocytosis have a

From [a]the Department of Internal Medicine, Division of Allergy and Immunology, University of Michigan; [b]the Department of Internal Medicine I, Division of Hematology and Hemostaseology, Medical University of Vienna and Ludwig Boltzmann Cluster Oncology; and [c]the Laboratory of Allergic Disease, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda.

*Dr Akin is currently affiliated with the Department of Medicine, Division of Rheumatology, Allergy and Immunology, Brigham and Women's Hospital, Boston, Mass.

Supported by the Division of Intramural Research, National Institute of Allergy and Infectious Diseases, and grants #P21173-B13 and #SFB-F01820 of the Fonds zur Förderung der Wissenschaftlichen Forschung in Österreich (FWF).

Disclosure of potential conflict of interest: C. Akin receives research support from the Food Allergy Initiative, has provided legal consultation/expert witness testimony in cases related to anaphylaxis, and is on the Medical Advisory Board for the Mastocytosis Society. P. Valent receives research support from Novartis and Bristol-Myers Squibb. D. D. Metcalfe receives research support from the Division of Intramural Research, National Institute of Allergy and Infectious Diseases, and is a member of the Editorial Board for the World Allergy Organization.

Received for publication August 11, 2009; revised August 25, 2010; accepted for publication August 30, 2010.

Available online October 28, 2010.

Reprint requests: Dean D. Metcalfe, MD, NIH/NIAID/LAD, Building 10/11C207, 10 Center Dr, MSC 1881, Bethesda, MD 20892-1881. E-mail: dmetcalfe@niaid.nih.gov.

0091-6749
doi:10.1016/j.jaci.2010.08.035

much higher than expected accumulative prevalence of idiopathic hypotension that is reminiscent of idiopathic anaphylaxis.[9] This led investigators to examine patients given a diagnosis of episodes of unexplained hypotension to determine whether some subjects within this group might have had minor criteria for mastocytosis or occult mastocytosis. This indeed turned out to be the case.[10] The hypothesis was further strengthened by experimental data that demonstrated that a common adaptor molecule, termed non–T-cell activation linker, could be phosphorylated at rest by KIT bearing the common D816V mutation observed in mastocytosis.[11] The hyperphosphorylation of non–T-cell activation linker then contributed to enhanced IgE-mediated mast cell activation.

Based on these findings and other data, this mastocytosis consensus conference discussed and accepted the concept of an MMAS.[8] The ability to diagnose this disorder was supported by a later report.[12] More recent studies documenting that patients with systemic hypotension associated with insect stings have mastocytosis or a monoclonal mast cell population further substantiated the concept.[13-15]

MAST CELLS AND MEDIATORS

Mast cells are derived from hematopoietic stem cells and undergo terminal differentiation in tissues.[16] They are found concentrated in locations, such as the mucosal and endothelial surfaces, where tissues interface with the external environment. This is consistent with the current understanding of mast cells as sentinels of innate and adaptive immune systems. Although the exact role of mast cells in maintaining a healthy homeostatic state is yet to be understood, mast cells most often come to clinical attention because of their involvement in allergic diseases.

Stem cell factor (SCF) is the major cytokine involved in mast cell growth and differentiation. SCF can also enhance IgE-mediated mast cell degranulation and act as a chemotactic factor.[16] SCF acts through KIT, a transmembrane receptor encoded by the proto-oncogene *c-Kit*, which has intrinsic tyrosine kinase activity. KIT is activated when it is cross-linked by SCF. Activation of KIT has also been shown to enhance IgE-mediated mast cell activation. The D816V point mutation results in constitutive activation of the tyrosine kinase domain of KIT and leads to SCF-independent autophosphorylation of the molecule.

Mast cells are thus activated by both IgE-dependent and IgE-independent mechanisms (see Table E2 in this article's Online Repository at www.jacionline.org). Regardless of the mechanism, activation of mast cells results in (1) degranulation with resulting release of preformed mediators stored in granules, including histamine, heparin, proteases, and cytokines, such as TNF-α; (2) *de novo* synthesis of arachidonic acid metabolites (most notably prostaglandin D_2 and leukotriene C_4) from membrane lipids; and (3) synthesis and secretion of cytokines and chemokines.[16]

CLASSIFICATION OF DISEASES ASSOCIATED WITH MAST CELL PROLIFERATION/ACTIVATION

Mast cells play a critical role in the genesis or perpetuation of a number of clinical diseases ranging from those associated with an intrinsic or primary defect in mast cells, such as occurs in mastocytosis, to diseases in which mast cells are recruited through a non–mast cell–dependent, extrinsic mechanism, resulting in a disease associated with "secondary" mast cell activation (Table I).

Diseases associated with primary mast cell activation

Currently, there are 2 well-characterized acquired molecular defects resulting in mast cell proliferation: a point mutation (D816V) in *c-Kit* associated with mastocytosis[17] and a rearrangement producing the FIP1-like 1/platelet derived growth factor receptor alpha (FIP1L-1-PDGFRA) fusion transcript[18] associated with chronic eosinophilic leukemia with increased mast cell numbers. The latter molecular defect results in a disease primarily manifested by symptoms attributable to eosinophilic proliferation.

Patients with systemic mastocytosis often have episodic symptoms of mast cell activation, such as flushing, lightheadedness, and gastrointestinal cramping.[7,8] However, there are patients with systemic mastocytosis who have no specific symptoms over years to decades, even if the mast cell burden is high.

The D816V *c-Kit* gain-of-function point mutation has been shown to be associated with more than 90% of adult cases of systemic mastocytosis.[7,8] Since its initial description, the diagnostic standard for systemic mastocytosis has been the demonstration of multifocal mast cell clusters of atypical morphology in a bone marrow biopsy specimen.[4] This characteristic finding has been accepted as the major diagnostic criterion for mast cell disease.[7] The minor diagnostic criteria for the disease include a tryptase level of greater than 20 ng/mL, atypical (spindle-shaped and hypogranulated) mast cell morphology, aberrant expression of CD2 and CD25 on mast cells, and detection of a codon 816 mutation in *c-Kit*. According to World Health Organization (WHO) guidelines, at least the major criterion plus 1 minor or 3 minor criterion are needed for the diagnosis of mastocytosis.[7] Typical skin lesions of urticaria pigmentosa (UP) are present in approximately 80% of patients with mastocytosis.

A group of patients with recurrent hypotension have recently been described to have clonal mast cells, as demonstrated by evidence of 1 or more minor criteria for mastocytosis, including aberrant mast cell morphology, CD25 expression, and/or the presence of the *c-Kit* D816V point mutation.[10] A recent consensus conference agreed that patients with only 1 or 2 minor criteria for mastocytosis have MMAS (Fig 1).[8] The characteristic clinical presentation of these patients includes episodic symptoms of mast cell degranulation, most commonly flushing, lightheadedness, and abdominal symptoms, such as cramping, nausea, and diarrhea. Symptoms might progress to loss of consciousness and life-threatening hypotension. The episodes can last for a few minutes to several hours. There are no identifiable triggers in most patients, although some events have been associated with Hymenoptera stings, eating, and exercise (with no food-specific IgE). These patients lack characteristic bone marrow mast cell clusters identified in mastocytosis (≥15 mast cells) and often have normal or only slightly increased serum tryptase levels. The D816V mutation might be only detectable in a bone marrow sample enriched for mast cells and not in peripheral blood or unfractionated bone marrow.[10] Careful morphologic examination of bone marrow mast cells in Wright-Giemsa–stained aspirates or in tryptase-stained biopsy sections might reveal hypogranulated and spindle-shaped mast cells, which can form small clusters (<15 mast cells) and display blood vessel or bone tropism. These patients thus have a disease process manifesting itself primarily as mast cell activation rather than mast cell proliferation, although they share similar pathologic features. Limited follow-up of this patient population thus far has not suggested progression of the extent of bone

TABLE I. Classification of diseases associated with mast cell activation

1. Primary
a. Hypotension with an associated clonal proliferative mast cell disorder (mastocytosis)
b. MMAS*
2. Secondary
a. Allergic disorders
b. Mast cell activation associated with chronic inflammatory or neoplastic disorders
c. Physical urticarias†
d. Chronic autoimmune urticaria
3. Idiopathic‡
a. Anaphylaxis
b. Angioedema
c. Urticaria
d. MCAS§

*See text for explanation.
†Requires a primary stimulation.
‡When mast cell degranulation has been documented, it might be either primary or secondary, and thus no longer idiopathic. Note also that angioedema might be associated with hereditary or acquired angioedema, where it could be mast cell independent and result from kinin generation.
§See text and Table II for proposed diagnostic criteria.

marrow mast cell infiltration, arguing against the possibility that these findings simply represent an early form of systemic mastocytosis. There is also convincing evidence that a significant number of patients who experience hypotension after Hymenoptera stings and have increased baseline tryptase levels either have (occult) systemic mastocytosis or bone marrow mastocytosis or meet the criteria for MMAS.[15]

Diseases associated with secondary mast cell activation

Secondary mast cell activation (Table I) occurs in allergic diseases. Symptoms can be infrequent to frequent, and resultant disease can be sporadic or chronic. Pathology follows aggregation of high-affinity IgE receptors by allergen-bound IgE.[19] Mast cells are also activated through non–IgE-mediated mechanisms, including IgG, complement, microbial components, drugs, hormones, physical stimuli, and cytokines. These mechanisms of mast cell activation are observed in patients with nonallergic inflammatory disorders, including chronic autoimmune urticaria, and in patients with physical urticarias (see Table E3 in this article's Online Repository at www.jacionline.org). IFN-γ specifically can induce human mast cells to upregulate high-affinity IgG receptors, cross-linking of which can cause mast cell degranulation.[20] This mechanism of mast cell activation might be operational in IFN-γ–rich autoimmune disease states, such as psoriasis, and in inflammatory bowel disease (see Table E3). C3a and C5a, activation products of the complement pathway, are capable of activating certain mast cell types (eg, skin mast cells and mast cells in patients with rheumatoid arthritis) by directly binding to their respective receptors on the mast cell surface.[20] Complement-induced mast cell activation can thus contribute to disease symptoms in infectious, autoimmune, and neoplastic diseases. Infectious agents also stimulate mast cells directly through Toll-like receptors recognizing molecular patterns common to microbial or viral pathogens.[16] Human mast cells have been shown to carry Toll-like receptors 1 to 7 and 9 and respond to Toll-like receptor stimulation through release of

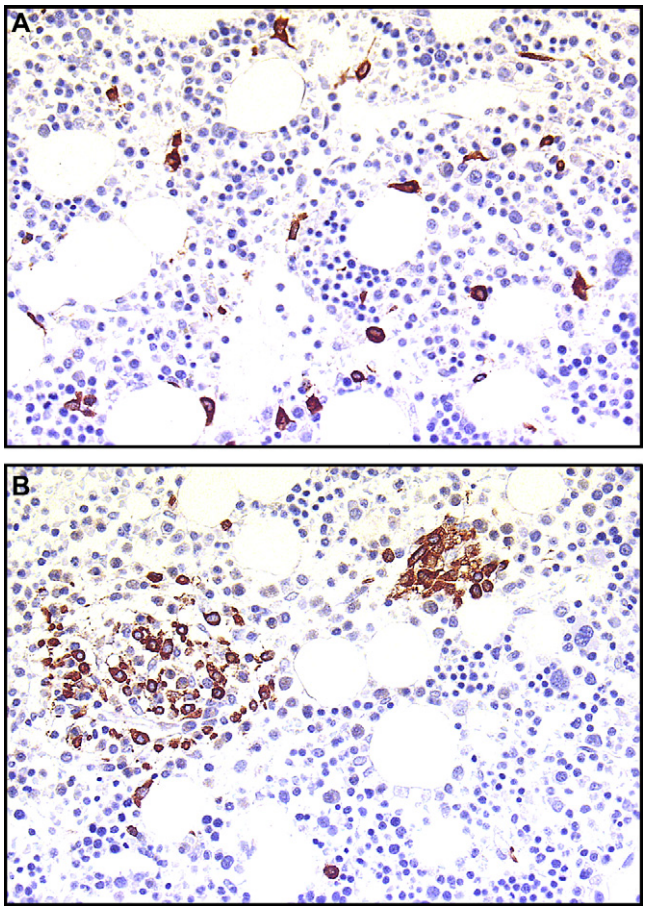

FIG 1. Bone marrow findings in patients with mast cell activation disorders. **A**, Tryptase-stained bone marrow sections revealed diffusely scattered spindle-shaped mast cells that did not form compact aggregates. **B**, Small-sized multifocal aggregates of mast cells were found, some of which contained 15 or more mast cells. Mast cells expressed CD25. Findings in Fig 1, *A*, are consistent with the diagnosis of an MMAS, whereas findings in Fig 1, *B*, are consistent with the diagnosis of systemic mastocytosis.

cytokines and leukotriene C_4.[21] Drugs such as opioid analgesics, adenosine, and vancomycin can induce pruritus, flushing, and bronchoconstriction by directly activating mast cells. Hypersensitivity reactions to nonsteroidal anti-inflammatory drugs inhibiting the COX pathway have been attributed to shifting of arachidonic acid metabolism to the 5-lipoxygenase pathway, causing symptoms because of overproduction of leukotrienes. If use of such a pharmacologic agent is associated with all episodes under question, the diagnosis then is one of an adverse reaction to a drug and not MCAS. However, if the administration of such an agent does not always precede an episode, then the patient could also have MCAS.

Idiopathic mast cell activation

Considering the well-established role mast cells play in urticaria, angioedema, and anaphylaxis, patients presenting with these disorders, in which there is no identifiable cause, have been included under the idiopathic category (Table I). However, the search must continue for the cause of these idiopathic disorders, including the possibility that mast cell activation in these disorders might relate to a yet-to-be-identified endogenous or

TABLE II. Proposed criteria for the diagnosis of MCAS*

1. Episodic symptoms consistent with mast cell mediator release affecting ≥2 organ systems evidenced as follows:
a. Skin: urticaria, angioedema, flushing
b. Gastrointestinal: nausea, vomiting, diarrhea, abdominal cramping
c. Cardiovascular: hypotensive syncope or near syncope, tachycardia
d. Respiratory: wheezing
e. Naso-ocular: conjunctival injection, pruritus, nasal stuffiness
2. A decrease in the frequency or severity or resolution of symptoms with antimediator therapy: H_1- and H_2-histamine receptor inverse agonists, antileukotriene medications (cysteinyl leukotriene receptor blockers or 5-lipoxygenase inhibitor), or mast cell stabilizers (cromolyn sodium)
3. Evidence of an increase in a validated urinary or serum marker of mast cell activation: documentation of an increase of the marker to greater than the patient's baseline value during a symptomatic period on ≥2 occasions or, if baseline tryptase levels are persistently >15 ng, documentation of an increase of the tryptase level above baseline value on 1 occasion. Total serum tryptase level is recommended as the marker of choice; less specific (also from basophils) are 24-hour urine histamine metabolites or PGD_2 or its metabolite 11-β-prostaglandin F_2.
4. Rule out primary and secondary causes of mast cell activation and well-defined clinical idiopathic entities in Table I.

PGD_2, Prostaglandin D_2.
*MCAS for now remains an idiopathic disorder; however, in some cases it could be an early reflection of a monoclonal population of mast cells, in which case with time it could meet the criteria for MMAS as 1 or 2 minor criteria for mastocytosis are fulfilled.

environmental stimulus, intrinsic mast cell defect, or both, resulting in a hyperactive mast cell phenotype.

It is also possible that some idiopathic events follow basophil activation rather than mast cell activation or result from activation of both mast cells and basophils. Selective activation of basophils might be explained by the differential expression of critical cell-surface receptors on basophils and mast cells. In fact, some triggers of mediator release might preferentially activate basophils.

PROPOSED CRITERIA FOR THE DIAGNOSIS OF IDIOPATHIC MCAS

The presence of a distinct idiopathic MCAS (Table I), when MMAS has been eliminated, has not been universally accepted. Despite the absence of a consensus for objective guidelines for diagnosis, this syndrome is assigned to some patients with a variable number of unexplained signs and symptoms (see Table E1) and with an otherwise negative diagnostic workup result.

We therefore propose that the diagnosis of MCAS is appropriate when primary and secondary diseases associated with mast cell activation and defined clinical idiopathic entities (Table I) are eliminated and if the 3 additional criteria in Table II are met. In the proposed diagnostic criteria, patients with a presumptive diagnosis of MCAS must have recurrent manifestations of mast cell activation involving 2 or more systems, such as flushing, diarrhea, and wheezing. The diagnosis requires that a patient has evidence of an increase in mediators such as serum tryptase, 24-hour urine N-methylhistamine, or prostaglandin D_2 or its metabolite 11-β-prostaglandin F_2 during at least 2 episodes with a negative workup result for systemic mastocytosis or clonal mast cell disease in bone marrow biopsy specimens or 1 episode in patients whose serum tryptase level is consistently greater than 15 ng/mL.[8] This requirement for biochemical evidence of mast cell activation is of importance to avoid applying the term MCAS to a diagnosis of a disorder unrelated to mast cell pathology but presenting with similar symptoms in the absence of biochemical proof of mast cell activation.

To illustrate this point, a patient with recurrent unexplained episodes of flushing, abdominal cramping, and hypotension would first have a bone marrow examination to determine whether there is evidence of a clonal mast cell disease. If the patient does not meet the criteria for a clonal mast cell disease, the clinical definition of idiopathic anaphylaxis according to consensus criteria would be considered.[22,23] In the absence of exposure to a known or likely antigen, the diagnosis of idiopathic anaphylaxis requires acute onset of disease with involvement of the skin, mucosal tissue, or both and either respirator compromise, such as dyspnea, bronchospasm, stridor, reduced peak expiratory flow rate, or hypoxemia, or reduced blood pressure or associated symptoms of end-organ dysfunction, such as hypotonia, syncope, or incontinence. If the patient's episodes do not meet the clinical criteria for idiopathic anaphylaxis and other well-defined clinical entities shown in Table I, the provisional diagnosis of MCAS might be considered.

Improvement of symptoms with drugs targeting mast cell mediators (eg, H_1- and H_2-antihistamines, cromolyn, and leukotriene antagonists) are considered as further supporting evidence of mast cell involvement in the disease process. However, response to antimediator therapy, although a diagnostic requirement, cannot be used alone. For instance, gastrointestinal mast cells degranulate in association with a number of disorders, and antihistamines, cromolyn, and leukotriene antagonists, if effective, do not necessarily implicate mast cells.

Patients presenting with signs and symptoms suggesting MCAS generally have undergone an extensive evaluation to rule out known disease. This being acknowledged, it is always necessary to review medical records of previous evaluations to ensure such assessments were sufficient to eliminate from consideration other diseases, including carcinoid syndrome and other malignant conditions, such as pheochromocytoma and medullary thyroid cancer, estrogen or testosterone deficiency, inflammatory bowel disease, autoimmune diseases, reactions to environmental toxins, and allergic reactions.

If previous medical evaluations did not identify a basis for the patient's symptoms, systemic mastocytosis or MMAS should then be considered. A careful skin examination should be performed to look for cutaneous mastocytosis, including UP. A basal serum tryptase level of greater than 20 ng/mL is a minor diagnostic criterion of systemic mastocytosis and should prompt consideration of systemic mastocytosis in patients who have evidence of mast cell activation. It is also worthy of note that tryptase levels might be increased in patients with other hematologic disorders, such as chronic eosinophilic leukemia, myelodysplastic syndromes, and acute leukemias.[24] Although tryptase levels increase transiently during mast cell activation, the tryptase level

in patients with systemic mastocytosis and other myeloid neoplasms is persistently increased.

A normal tryptase level does not rule out clonal mast cell disease. However, the likelihood of diagnosing mast cell disease by identifying characteristic multifocal bone marrow aggregates diminishes significantly in those with tryptase levels of less than 20 ng/mL. Furthermore, the diagnosis of systemic mast cell disease based on biopsies other than bone marrow should generally be avoided. As for a bone marrow evaluation, we are not suggesting that this study be performed in all pediatric patients with UP. This is because the diagnosis of UP establishes a diagnosis of primary mast cell disease, and patients with UP are excluded from being given a diagnosis of MMAS or MCAS. Because of these problems and others, difficult diagnostic cases should be considered for referral to a mast cell disease research and referral center for specialized testing, such as flow cytometry and mutational analysis, on marrow enriched for mast cells, approaches that might not be generally available. If clonal markers of mast cell disease are found (ie, *c-Kit* mutation or aberrant CD25 expression), the patient is assigned a diagnosis of systemic mastocytosis or MMAS depending on the presence or absence of other WHO diagnostic criteria, regardless of the presence of a secondary diagnosis, which might cause mast cell activation.[7,8]

Documentation of mast cell mediator release associated with symptomatic episodes provides critical information to support the premise that symptoms are due to mast cell activation. These tests include serum tryptase measurement (which should be obtained within 4 hours after the onset of symptoms) and 24-hour urine collections for N-methylhistamine and 11-β-prostaglandin F_2. Levels of these mediators during symptomatic periods must be compared with the patient's baseline values. Patients with increased mast cell mediator levels should be carefully evaluated for secondary causes of mast cell activation (Table I). If a patient meets the diagnostic criteria for systemic anaphylaxis as defined by consensus,[22,23] has no identifiable allergic or clonal mast cell cause, but has evidence of mast cell activation, we recommend this be acknowledged by noting that the diagnosis of idiopathic anaphylaxis is accompanied by evidence of mast cell activation. It might be with time as we understand the basis for MCAS that the diagnosis of a given idiopathic syndrome for some patients will be MCAS with systemic anaphylaxis, urticaria, and/or angioedema. For a comparison of diagnostic features for systemic mastocytosis, MMAS, MCAS, and idiopathic anaphylaxis, see Table E4 in this article's Online Repository at www.jacionline.org.[22,23]

Evaluation should include a repeat test of mediator levels after complete resolution of symptoms to determine whether the level returned to the patient's baseline value. If clonal markers are absent and a concurrent diagnosis of allergic, inflammatory, infectious, or neoplastic disease is established, then the patient should be considered to have a secondary mast cell activation disorder because of the concurrent illness. Using the approach outlined above, one of us (C. A.) has reported evidence that such a syndrome exists.[25] This study has now been extended using the proposed criteria. Although these data have not yet been published, of 132 patients enrolled in the protocol and referred for suspected or confirmed disease over a 4-year period, 58 met the WHO criteria for systemic mastocytosis, 7 for MMAS, and 19 for idiopathic anaphylaxis. Forty-two patients had mast cell activation symptoms but no evidence of clonal mast cells. Six patients had another diagnosis unrelated to mast cell disease. A second clinical study also supports the concept that there exists a group of patients with MCAS. Álvarez-Twose et al[26] recently published an in-depth analysis of 83 patients presenting with "severe and systemic mediators-related symptoms" in the absence of evidence of cutaneous mastocytosis. Fifty-one of these patients were given diagnoses of indolent systemic mastocytosis and 3 were given diagnoses of a "clonal mast cell activation disorder." The remaining 32 patients were said to have a "nonclonal mast cell activation disorder," the episodes of which were often associated with mediator release. Although 54% of these latter patients had episodes provoked by foods, drugs, and insect stings, the episodes occurring in the remaining 46% of this subset were judged to be "idiopathic" by the authors and thus appear consistent with a MCAS. This patient group also has an increased resting baseline tryptase level (see Table E4). Although the preponderance of data in both these studies relates to the adult population, future studies are envisioned in which the same criteria could be examined for validity in the pediatric population.

We believe that these criteria constitute a reasonable and objective starting point in an attempt to classify and diagnose MCAS. If the criteria are strictly applied, assigning a diagnosis of MCAS to patients with nonspecific symptoms without objective evidence of mast cell activation is avoided. For the future, in validating MCAS as a diagnosis, other evidence of mast cell degranulation *in vivo* using such techniques as electron microscopy[27] would be helpful, as has been done for exercise-induced anaphylaxis.[28]

SUMMARY

We believe that these recommendations for the diagnosis and management of MCAS form a starting point toward a global classification of mast cell disorders in general and MCAS in specific. To be generally acceptable, this classification scheme must be validated and modified by findings from prospective multicenter clinical studies.

REFERENCES

1. The Mastocytosis Society. What are the symptoms of mast cell diseases?. Available at: http://www.tmsforacure.org/mastocytosis.shtml. Accessed December 21, 2009.
2. Molderings GJ, Kolck UW, Scheurlen C, Bruss M, Homann J, Kugelgen IV. Multiple novel alterations in Kit tyrosine kinase in patients with gastrointestinally pronounced systemic mast cell activation disorder. Scand J Gastroenterol 2007;42:1045-53.
3. Roberts LJ. Carcinoid syndrome and disorders of systemic mast-cell activation including systemic mastocytosis. Endocrinol Metab Clin North Am 1988;17:415-36.
4. Metcalfe DD. Classification and diagnosis of mastocytosis: current status. J Invest Dermatol 1991;96:2S-4S.
5. Keffer JM, Bressler RB, Wright R, Kaliner MA, Metcalfe DD. Analysis of the wheal and flare reactions that follow the intradermal injection of histamine and morphine in adults with recurrent, unexplained anaphylaxis and systemic mastocytosis. J Allergy Clin Immunol 1989;83:595-601.
6. Roberts JL, Oates JA. Biochemical diagnosis of systemic mast cell disorders. J Invest Dermatol 1991;96:19S-25S.
7. Horny H-P, Metcalfe DD, Bennett JM, Bain BJ, Akin C, Escribano L, et al. Mastocytosis. In: Swerdlow SH, Campo E, Harris NL, Jaffee ES, Pileri SA, Stein H, editors. WHO classification of tumours of haematopoietic and lymphoid tissuesLyon: IARC Press; 2008. p. 54-63.
8. Valent P, Akin C, Escribano L, Fodinger M, Hartman K, Metcalfe DD, et al. Standards and standardization in mastocytosis: consensus statement on diagnostics, treatment recommendations and response criteria. Eur J Clin Invest 2007;37:435-53.

9. Brockow K, Jofer C, Behrendt H, Ring J. Anaphylaxis in patients with mastocytosis: a study on history, clinical features and risk factors in 120 patients. Allergy 2008;63:226-32.
10. Akin C, Scott LM, Kocabas CN, Kushnir-Sukhov N, Brittain E, Noel P, et al. Demonstration of an aberrant mast-cell population with clonal markers in a subset of patients with "Idiopathic" anaphylaxis. Blood 2007;110:2331-3.
11. Iwaki S, Spicka J, Tkaczyk C, Jensen BM, Furumoto Y, Charles N, et al. Kit- and Fc epsilonRI-induced differential phosphorylation of the transmembrane adaptor molecule NTAL/LAB/LAT2 allows flexibility in its scaffolding function in mast cells. Cell Signal 2008;20:195-205.
12. Sonneck K, Florian S, Müllauer L, Wimazal F, Födinger M, Sperr WR, et al. Diagnostic and subdiagnostic accumulation of mast cells in the bone marrow of patients with anaphylaxis: monoclonal mast cell activation syndrome. Int Arch Allergy Immunol 2007;142:158-64.
13. Ludolph-Hauser D, Rueff F, Fries C, Schopf P, Przybilla B. Constitutively raised serum concentrations of mast-cell tryptase and severe anaphylactic reactions to Hymenoptera stings. Lancet 2001;357:361-2.
14. Gonzalez de Olano D, Alverez-Twose I, Esteban-Lopez MI, Sanchez- Munoz L, de Durana MD, Vega A, et al. Safety and Effectiveness of immunotherapy in patients with indolent systemic mastocytosis presenting with Hymenoptera venom anaphylaxis. J Allergy Clin Immunol 2008;121:519-26.
15. Bonadonna P, Perbellini O, Passalacqua G, Caruso B, Colarossi S, Dal Fior D, et al. Clonal mast cell disorders in patients with systemic reactions to Hymenoptera stings and increased serum tryptase levels. J Allergy Clin Immunol 2009;123:680-6.
16. Metcalfe DD. Mast cell and mastocytosis. Blood 2008;12:946-56.
17. Nagata H, Worobec AS, Oh CK, Chowdhury BA, Tannenbaum S, Suzuki Y, et al. Identification of a point mutation in the catalytic domain of the protooncogene c-kit in peripheral blood mononuclear cells of patients who have mastocytosis with an associated hematologic disorder. Proc Natl Acad Sci U S A 1995;92:10560-4.
18. Gotlib J, Cools J. Five years since the discovery of FIP1L1-PDGFRA: what we have learned about the fusion and other molecularly defined eosinophilias. Leukemia 2008;22:1999-2010.
19. Brown JM, Wilson TM, Metcalfe DD. The mast cell and allergic diseases: role in pathogenesis and implications for therapy. Clin Exp Allergy 2007;38:4-18.
20. Woolhiser MR, Brockow K, Metcalfe DD. Activation of human mast cells by aggregated IgG through FcγR1: effects of C3a. Clin Immunol 2004;119:172-80.
21. Kulka M, Alexopoulou L, Flavell RA, Metcalfe DD. Activation of mast cells by double-stranded RNA: evidence for activation through toll-like receptor-3 (TLR-3). J Allergy Clin Immunol 2004;114:174-82.
22. Sampson HA, Muñoz-Furlong A, Bock SA, Schmitt S, Bass R, Chowdhury BA, et al. Symposium on the definition and management of anaphylaxis: summary report. J Allergy Clin Immunol 2005;115:584-91.
23. Sampson HA, Muñoz-Furlong A, Campbell RL, Adkinson NF, Bock SA, Branum A. Second symposium on the definition and management of anaphylaxis: Summary report–Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol 2006; 117:391-7.
24. Sperr WR, El-Samahi A, Kundi M, Girschikofsky M, Winkler S, Lutz D, et al. Elevated tryptase levels selectively cluster in myeloid neoplasms: a novel diagnostic approach and screen marker in clinical haematology. Eur J Clin Invest 2009;39: 914-23.
25. Kassab D, Koterba A, Jiang Y, Akin C. Elevated tryptase levels in patients with mast cell activation syndromes without evidence of mastocytosis. J Allergy Clin Immunol 2008;121(suppl):S67.
26. Álvarez-Twose I, González de Olano D, Sánchez-Muñoz L, Matito A, Esteban-López M, Vega A, et al. Clinical, biological, and molecular characteristics of clonal mast cell disorders presenting with systemic mast cell activation syndrome. J Allergy Clin Immunol 2010;125:1269-78, e2.
27. Dvorak AM. ultrastructure of mast cells and basophils. In: Ring J, Adorini L, Berek C, Blaser K, Capron M, Denburg JA, editors. Chemical immunology and allergy, vol. 85. Basel: Karger; 2005. p. 135-84.
28. Sheffer AL, Tong AK, Murphy GF, Lewis RA, McFadden ER Jr, Austen KF. Exercise-induced anaphylaxis: a serious form of physical allergy associated with mast cell degranulation. J Allergy Clin Immunol 1985;75:479-84.

Correction

With regard to the online version of the September 2010 article entitled "The diagnosis and management of anaphylaxis practice parameter: 2010 update" (J Allergy Clin Immunol 2010;126:477-480.e42), on page 480.e11, in the fifth bulleted paragraph on the page, the amount of epinephrine in 100 mL of saline is incorrect as given. The sentence should read as follows: "…a 1:100,000 solution of epinephrine (1.0 mg [1 mL of 1:1000] in 100 mL saline)…" In addition, in the Executive Summary of the practice parameter, which appears in the print version of the Journal, the grading system for the statements was inadvertently omitted. This system is presented in the online version of the full document. Each of the summary statements was followed by a letter in parentheses that reflected the level of evidence that supported that statement. For example, "(B)" means that the statement was directly based on category II evidence or extrapolated from category I evidence. The criteria for each category of evidence can be seen in the following table:

Classification of Recommendations and Evidence

Category of evidence:	
Ia	Evidence from meta-analysis of randomized controlled trials
Ib	Evidence from at least one randomized controlled trial
IIa	Evidence from at least one controlled study without randomization
IIb	Evidence from at least one other type of quasi-experimental study
III	Evidence from non-experimental descriptive studies, such as comparative studies
IV	Evidence from expert committee reports or opinions or clinical experience of respected authorities or both
Strength of recommendation:	
A	Directly based on category I evidence
B	Directly based on category II evidence or extrapolated from category I evidence
C	Directly based on category III evidence or extrapolated from category I or II evidence
D	Directly based on category IV evidence or extrapolated from category I, II, or III evidence
E	Based on consensus of the Joint Task Force on Practice Parameters

TABLE E1. Signs and symptoms suggested to potentially occur in MCAS or mast cell activation disorder*

I. Systemic	VI. Gastrointestinal
Anaphylaxis	Nausea
Faintness	Vomiting
Fatigue	Abdominal pain
II. Dermatologic	Gastroesophageal reflux
Flushing	Diarrhea
Rashes	Inflammation of the esophagus
Itching	Intestinal cramping and bloating
Hives	Malabsorption
III. Cardiovascular	VII. Neurologic
Blood pressure changes and shock	Cognitive difficulties/brain fog
Chest pain	Dizziness/vertigo
Rapid heart rate	Lightheadedness
IV. Pulmonary	Migraine headache
Wheezing	Paresthesia
V. Musculoskeletal	Peripheral neuropathy
Bone pain	
Muscle pain	
Degenerative disc disease	
Osteoporosis/osteopenia	

*Adapted from the Mastocytosis Society Web site.[1] These symptoms are attributed to mast cell degranulation in mastocytosis, and those with mast cell activation disorder/MCAS are said to have many of the same symptoms.

TABLE E2. Selected mast cell activators of clinical relevance

1. IgE dependent
a. Allergen
b. Anti-IgE IgG
2. IgE independent
a. IgG through FcεRI
b. Anti-FcεRI IgG
c. Bacterial components
I. Peptidoglycan: TLR2/6
II. LPS: TLR4
III. fMLP
d. C3a, C5a
e. Cytokines/chemokines
I. SCF, NGF, MIP-1α
f. Neuropeptides
g. Drugs
I. Opioids, muscle relaxants, radiocontrast material, adenosine
h. Physical stimuli
I. Heat, cold, pressure
i. Hormones
I. Estrogen, progesterone, α-MSH, CRH

α-MSH, α-Melanocyte–stimulating hormone; *CRH*, corticotropin-releasing hormone; *fMLP*, formyl-methionyl-leucyl-phenylalanine; *MIP-1α*, macrophage inflammatory protein 1α; *NGF*, nerve growth factor; *TLR*, Toll-like receptor.

TABLE E3. Disease states associated with evidence of mast cell activation

Disease	Potential mechanisms
1. Atopic disease	Allergen-specific IgE
2. Chronic autoimmune urticaria	Anti-IgE or anti-FcϵRI autoantibodies
3. Autoimmunity	IgG receptor, complement
4. Chronic infections	TLRs, IgG, complement
5. Drug allergy	Specific receptors, complement, IgE
6. Physical stimuli	Direct mast cell activation
7. Neoplasms	Complement, cytokines

TLR, Toll-like receptor.

TABLE E4. Comparison of clinical and diagnostic features for SM, MMAS, MCAS, and IA

	SM	MMAS	MCAS	IA*
Baseline tryptase	>20	Normal or mildly increased	Normal or mildly increased	Normal
c-kit D816V	+	+	−	−
Multifocal mast cell aggregates	+	−	−	−
Aberrant CD25	+	+	−	−
UP	+/−	−	−	−
Mediator release symptoms	+	+	+	+
Hypotensive episodes	+/−	+/−	+/−	+/−
Urine N-MH or PGD_2	Increased at baseline	Increased during symptoms	Increased during symptoms	Increased during symptoms
Response to antimediator therapy	+	+	+	+/−

For complete diagnostic criteria, see references Sampson et al.[22,23]

IA, Idiopathic anaphylaxis; *N-MH*, N-methylhistamine; *SM*, systemic mastocytosis.